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Attestation

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

Den Haag, den
The Hague,
La Haye, le 20. 09. 2004

Der Präsident des Europäischen Patentamts
Im Auftrag
For the President of the European Patent Office
Le Président de l'Office européen des brevets
p.o.

F. v.d. Krogt

Patentanmeldung Nr.
Patent application no.
Demande de brevet n° PCT/EP 03/07537

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Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Arpida 5/A4

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ARPIDA 5/A4

Novel Benzofuran Derivatives

The present invention relates to novel 2,4-diamino-5-(substituted) pyrimidines, to pharmaceutical compositions containing them, to processes for preparing them and their compositions, to intermediates for making them and to their use in the treatment of microbial infections.

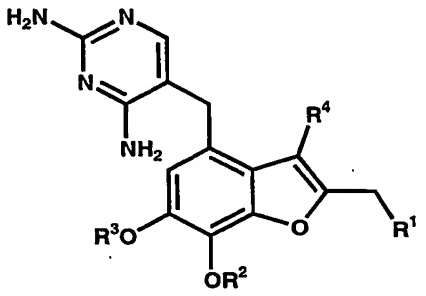
Certain 2,4-diamino-5-benzylpyrimidines have been demonstrated to be potent inhibitors of dihydrofolate reductase (DHFR), which catalyses the reduction of dihydrofolic acid to tetrahydrofolic acid (THFA). This property has been shown to result frequently in useful pharmaceutical properties particularly in the treatment of bacterial infections. Thus, U.K. Patent Specification No. 875,562 discloses *inter alia* 2,4-diamino-5-benzylpyrimidines wherein the benzyl moiety is substituted by three C_{1-4} alkoxy groups.

Trimethoprim, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, is specifically disclosed in U.K. Patent No. 875, 562 and is the most active antibacterial agent amongst the 2,4-diamino-5-benzylpyrimidines known to date. Due to their mode of action, these benzylpyrimidines potentiate the antibacterial activity of the sulphonamides, and Trimethoprim has been used extensively over the last decade in human therapy in combination with various sulphonamides, and in particular with sulphamethoxazole, for the treatment of bacterial infections.
European Patent Applications Nos. 81109631.2 and 83104240.3 disclose *inter alia* also such type of compounds and their use.
In WO 02/10157 similar compounds are described. However, the compounds disclosed hereinafter exhibit a much more potent activity against DHFR including mutated enzyme, a superior bioavailability, and a superior antibacterial activity.

It has now been found that a group of novel benzofuran derivatives are more potent than, e. g.,Trimethoprim, and are active against Gram positive pathogens (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis* or *Streptococcus pneumoniae*) and Gram negative pathogens (*Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Moraxella Cattharalis* or *Proteus vulgaris*). Furthermore, and as mentioned above, the compounds of formula I show a much

more potent activity against DHFR including mutated enzyme, a superior bioavailability, and a superior antibacterial activity.

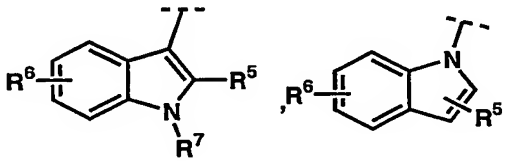
Therefore, the present invention relates to novel compounds of the general formula I



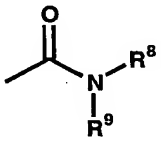
Formula I

wherein

R1 represents the groups



whereby in these groups R^5 is hydrogen, lower alkyl with 1 to 4 carbon atoms, or the group



R^8 represents hydrogen, lower alkyloxy, lower alkylamino, lower alkyl with 1 to 4 carbon atoms;

R^9 represents hydrogen, lower alkyl with 1 to 4 carbon atoms;

R^8 and R^9 together form a 5- or 6- membered heterocyclic ring containing one to two hetero atoms which can be the same or different and are oxygen or nitrogen.

R^6 represent hydrogen, halogen, nitro, lower alkyloxy, or boronic acid;

R^7 represents hydrogen;

R^2 and R^3 independently represent hydrogen; lower alkyl with 1 to 3 carbon atoms; or together a lower alkylene group with 1 to 3 carbon atoms bridging the oxygen atoms and forming a five, six or seven membered ring;

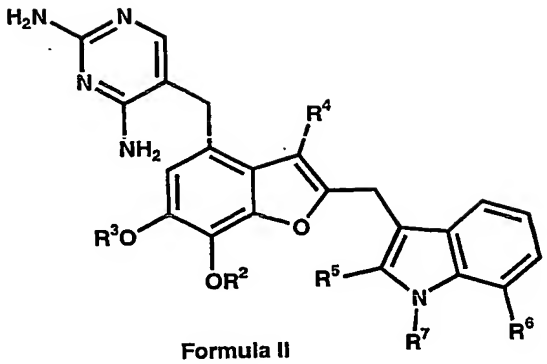
R^4 represents hydrogen, lower alkyl with 1 to 4 carbon atoms;

and pharmaceutically acceptable salts thereof.

In the definitions of the general formula **I** – if not otherwise stated – the expression lower ***alkyl*** means straight and branched alkyl chain groups with one to six carbon atoms, preferably 1 to 4 carbon atoms. Examples of lower alkyl and lower alkoxy groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.- butyl, tert.-butyl. These lower alkyl groups may be substituted with halogen atoms or hydroxy, thiol or lower alkoy groups. Examples are trifluoromethyl, chloromethyl, fluoromethyl, hydroxymethyl, thiomethyl, methoxy, ethoxy, propoxy, butoxy, iso-butoxy, sec.-butoxy and tert.-butoxy. The expression ***heterocyclic ring*** represents saturated and unsaturated, but not aromatic, five- or six-membered rings containing one to two hetero atoms which may be the same or different and are nitrogen, oxygen or sulfur atoms. Examples are piperidinyl, mopholinyl, piperazinyl, pyrrolidinyl, dihydroimidazolyl, dihydropyrazoyl, pyrazolidinyl or dihydroxazolinyl.

The expression halogen means fluorine, chlorine, bromine, and iodine but fluorine, chlorine and bromine are preferred.

One preferred group of compounds of the present invention are compounds of the general formula **II**



Formula II

wherein

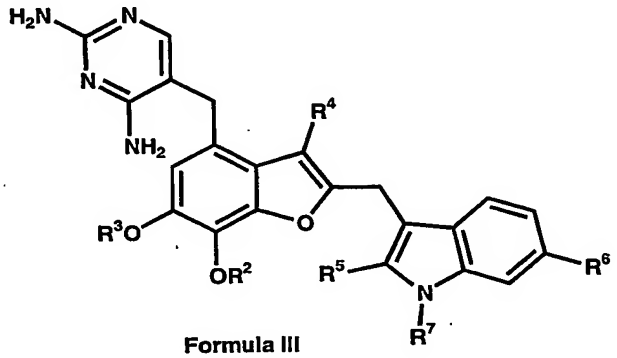
R^2 and R^3 represent methyl;

R^4 represents hydrogen;

R^5 and R^6 are as defined in formula I and;

R^7 represents hydrogen.

A further preferred group of compounds of the present invention are compounds of the general formula **III**



Formula III

wherein

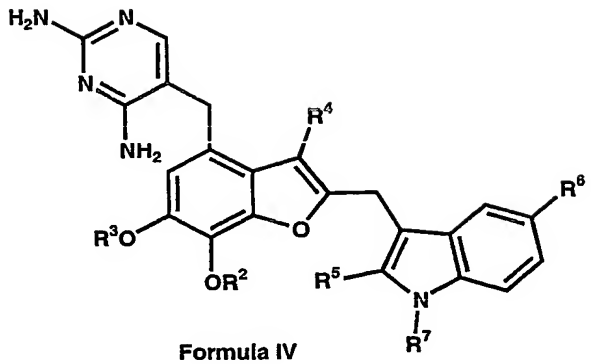
$R^2$and R^3 represent methyl;

R^4 represents hydrogen and

R^5 and R^6 are as defined in formula I and;

R^7 represents hydrogen.

A further preferred group of compounds of the present invention are compounds of the general formula **IV**



Formula IV

wherein

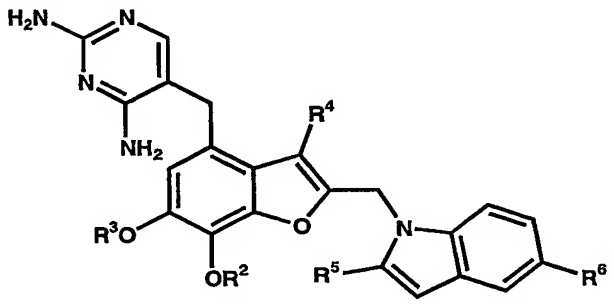
$R^2$and R^3 represent methyl;

R^4 represents hydrogen

R^5 and R^6 are as defined in formula I and;

R^7 represents hydrogen.

A further preferred group of compounds of the present invention are compounds of the general formula V



Formula V

wherein

R^2 and R^3 represent methyl;

R^4 represents hydrogen and

R^5 and R^6 are as defined in formula I;

Preferred compounds are compounds of formula **I**, **II**, **III**, **IV** and **V** wherein R^5 is hydrogen, methyl, carboxylic acid dimethylamide, carboxylic acid methoxymethylamide, pyrrolidin-1-yl-methanone, morpholin-4-yl-methanone;

R^6 represent hydrogen, fluoro, chloro, bromo, methoxy, methyl amine, nitro, boronic acid;

Especially preferred compounds are compounds selected from the group consisting of:

5-(2-Indol(4-boronicacid)-1-ylmethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine;

5-(2-Indol-1-ylmethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine;

5-[6,7-Dimethoxy-2-(7-methoxy-indol-1-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

5-[6,7-Dimethoxy-2-(5-methoxy-1-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

5-[2-(1-Indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

5-[6,7-Dimethoxy-2-(2-methyl-1-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

5-[2-(5-Bromo-indol-1-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

5-[2-(6-Fluoro-1-indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

{3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl}-morpholin-4-yl-methanone;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-5-boronic acid;

5-[6,7-Dimethoxy-2-(5-nitro-1H-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

{3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl}-pyrrolidin-1-yl-methanone;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-methoxy-1H-indole-2-carboxylic acid dimethylamide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide;

5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide;

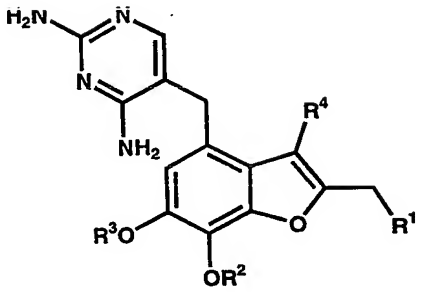
3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid dimethylamide;

5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid N,N'-dimethyl-hydrazide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid methoxy-methyl-amide;

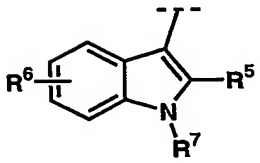
The invention also relates to a process for the manufacture of compounds of the general formula **I**



Formula I

wherein

R^1 represents the group



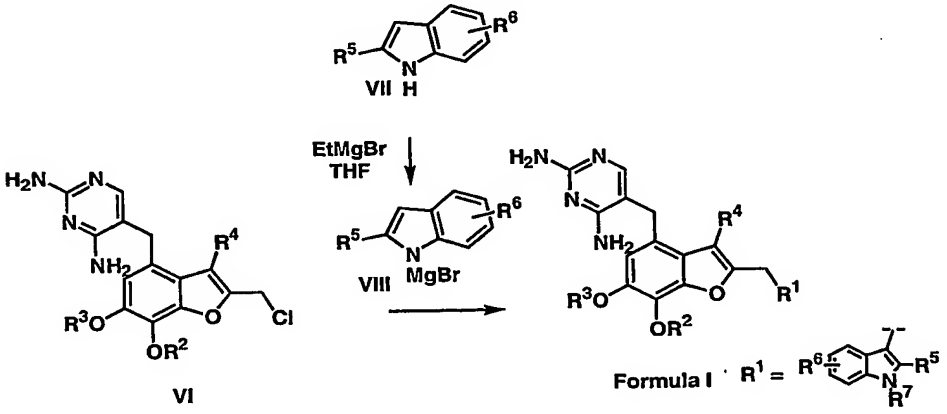
wherein

R^7 represents hydrogen

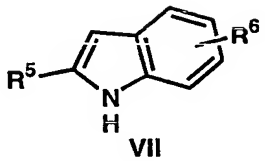
R^2, R^3, R^4, R^5 and R^6 have the meaning given in formula **I** above

which process comprises reacting – as depicted in **Scheme 1** – a compound of the general formula **VI** (see PCT Publication WO 02/10157), with the MgBr salt **VIII** of the corresponding indoles **VII**.

Scheme 1

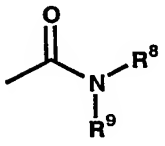


Some of the indoles of general formula **VII,**



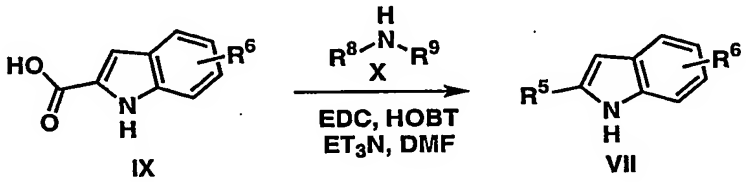
VII

wherein R^5 represents the group



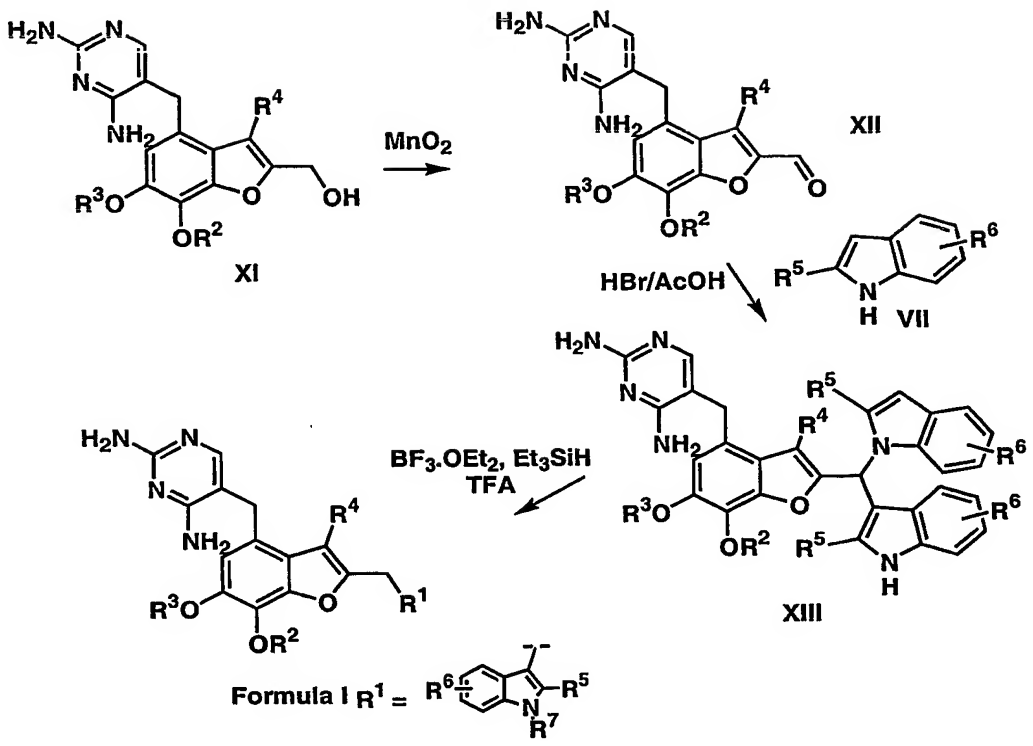
and R^6, R^8 and R^9 have the meaning given in formula **I** above, are synthesised by reacting the indoles **IX** with the corresponding amine **X** using EDC and HOBT as activating reagents as described in **Scheme 2.** The indoles **VII** so obtained are coupled to the compounds **VI** using the same procedure as described above in **Scheme 1** to give the compound of general formula **I.**

Scheme 2



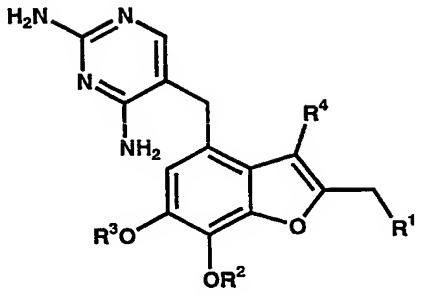
Access to an alternative array of substituents can be achieved by proceeding according to **Scheme 3**

Scheme 3



The intermediates of the general formula **XII** and **XIII** are novel compounds which serve as intermediates in the synthesis of active compounds of general formula **I**. The alcohol **XI** (see PCT Publication WO 02/10157) was oxidised to the aldehyde **XII** with MnO_2 and further coupling under acidic conditions (HBr in acetic acid) with the indoles **VII** resulted in the dimeric compounds of general formula **XIII**. Reduction of compounds **XIII** using trifluoroborane etherate and triethylsilane gave the compound of general formula **I** as described in **Scheme 3**

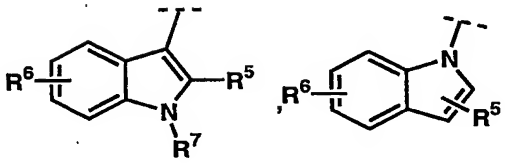
The invention also relates to a process for the manufacture of compounds of the general formula **I**



Formula I

wherein

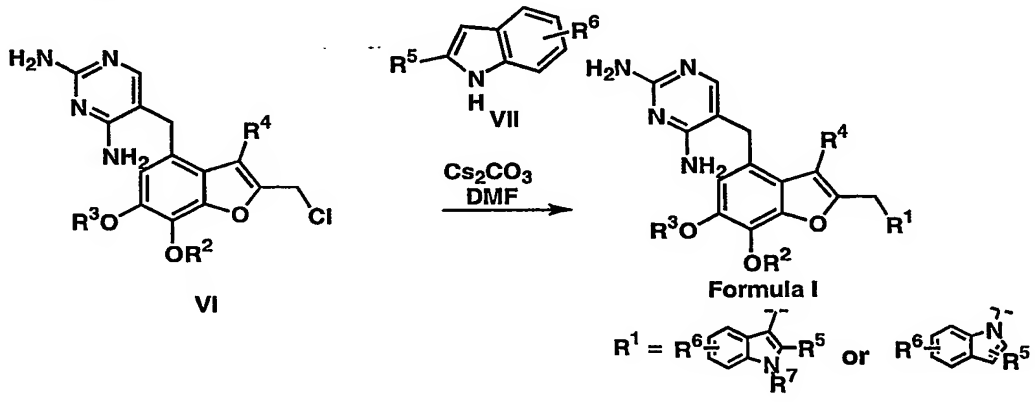
R^1 represents the group



and R^2, R^3, R^4, R^5 and R^6 have the meaning given in formula **I** above,

which process comprises reacting – as depicted in **Scheme 4** – a compound of the general formula **VI** (see PCT Publication WO 02/10157), with the corresponding indole moiety **VII** under basic conditions.

Scheme 4



Experimental part

Abbreviations:

ACN: Acetonitrile
ATCC: American type culture collection
DMF: Dimethyl formamide
DMSO: dimethyl sulfoxide
EtOH: Ethanol
ESI: Electrospray ionisation
FC. Flash chromatography
HPLC: High performance liquid chromatography
MeOH: methanol
MS: Mass spectrometry
NMR: Nuclear magnetic resonance
TBME: tert-Butyl methyl ether
TFA : Trifluoroacetic acid
THF: Tetrahydrofuran
TLC: Thin layer chromatography
EDC: N-Ethyl-N'(3-dimethylaminopropyl)carbodiimide hdrochoric acid salt
HOBT: 1-Hydroxybenzotrialzole
Eq.: equivalent

The preparation of indoles **VII** which are not described in the following examples are known from the references: Young, J. Chem. Soc. 1958, 3493-3494; Finger et al. J. Amer. Chem. Soc. 1959, 81, 94-97; Dekhane M., Dodd, R. H., Tetrahedron, 1994, 50, 21, 6299-6306.

General procedure A : Amide coupling (Scheme 2)

Under nitrogen, at room temperature and in a flask adapted with a mechanical stirrer, indole-carboxylic acid **IX** (1 eq.) was dissoveld in DMF. To this solution, the corresponding amine **X** (1.1 to 5 eq.) EDC (1.2 eq), HOBT (1,2 eq) and were added followed by triethylamine (3 eq.).The mixture was stirred overnight at room temperature. Atfer the reaction is completed, the mixture was poured slowly to a NaHCO3 solution. After extration with dichloromethane the organic layer was washed with 1 N HCl, and brien, dried on MgSO4 and evaporated under reduced pressure.

The compound **VII** was obtained as a solid and was used without further purification.

Example 1:

5-Chloro-1H-indole-2-carboxylic acid dimethylamide (633mg, 55%) was obtained by reacting 5-chloro-1H-Indole-2-carboxylic acid (1.0g, 5.10 mmol) with dimethylamine hydrochloride (500mg, 6.13 mmol), EDC (1.175g, 6.13mmol) and HOBT (826mg, 6.13mmol).

MS ESI : 223.0 (M+H).

Example 2:

5-Fluoro-1H-indole-2-carboxylic acid dimethylamide (791mg, 69%) was obtained by reacting 5-fluoro-1H-Indole-2-carboxylic acid (1.0g, 5.60 mmol) with dimethylamine hydrochloride (550mg, 6.72 mmol), EDC (1.30g, 6.72mmol) and HOBT (910mg, 6.72mmol).

MS ESI : 206.0 (M+H).

Example 3:

5-Chloro-1H-indole-2-carboxylic acid N,N'-dimethyl-hydrazide (937mg, 92%) was obtained by reacting 5-chloro-1H-Indole-2-carboxylic acid (1.0g, 6.20 mmol) with N,N'-dimethyl-hydrazine (980mg, 7.40 mmol), EDC (1.43g, 7.40mmol) and HOBT (1.01g, 7.40mmol).

MS ESI : 238.0 (M+H).

Example 4:

5-Fluoro-1H-indole-2-carboxylic acid methoxy-methyl-amide (2.85 g, 76%) was obtained by reacting 5-fluoro-1H-Indole-2-carboxylic acid (3.0 g, 16.74 mmol) with O,N-dimethyl-hydroxylamine (2.45 g, 25.11 mmol), EDC (3.85 g, 20.09 mmol) and HOBT (2.71 g, 20.09 mmol).

MS ESI : 223.0 (M+H).

Example 5:

5-Chloro-1H-indole-2-carboxylic acid methoxy-methyl-amide (952 mg, 78%) was obtained by reacting 5-chloro-1H-Indole-2-carboxylic acid (1.0 g, 5.10 mmol) with O,N-dimethyl-hydroxylamine (600 mg, 6.13 mol), EDC (1.17 g, 6.13 mmol) and HOBT (826 mg, 6.13 mmol).

MS ESI : 239.0 (M+H).

General procedure B: Coupling of the indols with compound V (Scheme 4)

To a solution of **VII** (1.1 eq) in dimethylformamide, cesium carbonate (3.0 eq) or potassium carbonate was added portionwise at room temperature under argon. Compound **VI** (1.0 eq) was added and the mixture was stirred for 2 hours at room temperature until completion. The reaction mixture was quenched with a solution saturated of $NaHCO_3$ and extracted with dichloromethane. The organic layer was washed with water, solution saturated of NaCl, dried over $MgSO_4$ and evaporated under reduced pressure. The compound **I** was obtained after purification by FC, gradient from CH_2Cl_2 to CH_2Cl_2/methanol (9/1).

Example 6:
5-[2-(1-Indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine (40 mg, 23%) was obtained as a brown solid by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (153 mg, 0.397 mmol) with cesium carbonate (388 mg, 1.19 mmol) and indole (51 mg, 0.437 mmol).
MS ESI : 430.2 (M+H); Structure confirmed by ^1H NMR 400 MHz in DMSO.

Example 7:
5-(2-Indol-1-ylmethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine diamine (39%) was obtained as a brown solid by reacting at 60°C 5-(2-Chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (501 mg, 1.302 mmol) with cesium carbonate (2.01 g, 5.208 mmol) and indole (305 mg, 2.604 mmol).
MS ESI : 430.2 (M+H); Structure confirmed by ^1H NMR 400 MHz in DMSO.

Example 8:
5-[6,7-Dimethoxy-2-(7-methoxy-indol-1-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine (120 mg, 62%) was obtained as a yellow solid by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (163 mg, 0.342 mmol) with cesium carbonate (413 mg, 1.26 mmol) and 7-Methoxy-1H-indole (68 mg, 0.465 mmol).
MS ESI : 460.2 (M+H).

Example 9:
5-[6,7-Dimethoxy-2-(5-methoxy-1-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine (30 mg, 18%) was obtained as a brown solid by reacting 5-(2-

chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (140 mg, 0.363 mmol) with cesium carbonate (355 mg, 1.09 mmol) and 5-methoxy-1H-indole (59 mg, 0.400 mmol).
MS ESI : 460.2 (M+H).

Example 10:
5-[6,7-Dimethoxy-2-(2-methyl-1-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine (27 mg, 16%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (151 mg, 0.392 mmol) with cesium carbonate (383 mg, 1.17 mmol) and 2-methyl-1H-indole (56 mg, 0.431 mmol).
MS ESI : 444.2 (M+H).

Example 11:
5-[2-(5-Bromo-indol-1-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine (76 mg, 41%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (143 mg, 0.371 mmol) with cesium carbonate (429 mg, 1.114 mmol) and 5-bromo-1H-indole (80 mg, 0.408 mmol).
MS ESI : 508.0/510.0 (M+H).

Example 12:
5-[2-(6-Fluoro-1-indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine (31 mg, 13%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (202 mg, 0.524 mmol) with cesium carbonate (607 mg, 1.573 mmol) and 6-fluoro-1H-indole (78 mg, 0.577 mmol).
MS ESI : 448.2 (M+H).

Example 13:
3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-5-boronic acid (5 mg, 3%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (129 mg, 0.334 mmol) with cesium carbonate (436 mg, 1.340 mmol) and indole-5-boronic acid (54 mg, 0.334 mmol).
MS ESI : 474.2 (M+H).

General procedure C: Coupling of the indols with compound V (Scheme 1)

To a suspension of **VII** (6.0 eq) in tetrahydrofurane freshly distilled, a 4.2M-solution of ethyl magnesium bromide in diethyl ether (6.0 eq) was added at 0°C under an argon flux. After stirring 1 hour at 0°C, diethyl ether was added to the resulting mixture to give the compound **VIII** as a beige precipitate. After decantation, the excess of solvent was removed and the compound **VIII** was suspended in dichloromethane.
To this suspension, the compound **VI** (1.0 eq) was added portionwise at room temperature under argon and the mixture was stirred overnight. The reaction was complete after stirring 16 hours at room temperature. The resulting mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with a solution saturated of $NaHCO_3$, with a solution saturated of NaCl, dried over $MgSO_4$ and evaporated. The compound **I** was obtained after purification by FC, gradient from CH_2Cl_2 to CH_2Cl_2/methanol (9/1).

Example 14:
{3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl}-morpholin-4-yl-methanone (42mg, 15%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (197 mg, 0.511 mmol) with a 4.2M-solution of ethyl magnesium bromide in diethyl ether (0.716 mL, 3.07 mmol) and (1H-indol-2-yl)-morpholin-4-yl-methanone (706 mg, 3.07 mmol). MS ESI : 543.1 (M+H).

Example 15:
3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide (43mg, 17%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (191 mg, 0.496 mmol) with a 4.2M-solution of ethyl magnesium bromide in diethyl ether (0.695 mL, 2.97 mmol) and 1H-indole-2-carboxylic acid dimethylamide (560 mg, 2.97 mmol). MS ESI : 501.2 (M+H); Structure confirmed by ^1H NMR 400 MHz in DMSO.

Example 16:
5-[6,7-Dimethoxy-2-(5-nitro-1H-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine (48mg, 26%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (153 mg, 0.389 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (0.783 mL, 2.33 mmol) and 5-nitro-1H-indole (379 mg, 2.33 mmol).

MS ESI : 475.2 (M+H).

General procedure D: Coupling of the indols with compound V (Scheme 1)

To a suspension of **VII** (6.0 eq) in tetrahydrofurane freshly distilled, a 4.2M-solution of ethyl magnesium bromide in diethyl ether (6.0 eq) was added at 0°C under an argon flux. After 1 hour at this temperature, diethyl ether was added to the resulting mixture to give the compound **VIII** as a beige precipitate. After decantation, the excess of solvent was removed and the compound **VIII** was suspended in dichloroethane.
To this suspension, the compound **VI** (1.0 eq) was added portionwise at room temperature under argon, zinc chloride (1 eq) was added and the reaction mixture was heated at 70 °C until the reaction was complete. The resulting mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with a solution saturated of $NaHCO_3$, with a solution saturated of NaCl, dried over $MgSO_4$ and evaporated. The compound **I** was obtained after purification by FC, gradient from CH_2Cl_2 to CH_2Cl_2/methanol (9/1).

Example 17:
{3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl}-pyrrolidin-1-yl-methanone (34 mg, 18%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (136 mg, 0.355 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (0.710 mL, 2.13 mmol), zinc chloride (48 mg, 0.355 mmol) and (1H-indol-2-yl)-pyrrolidin-1-yl-methanone (457 mg, 2.13 mmol).
MS ESI : 527.1 (M+H).

Example 18:
3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-methoxy-1H-indole-2-carboxylic acid dimethylamide (18 mg, 11%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (113 mg, 0.295 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (0.590 mL, 1.77 mmol), zinc chloride (40 mg, 0.295 mmol) and 5-methoxy-1H-indole-2-carboxylic acid dimethylamide (386 mg, 1.77 mmol).
MS ESI : 531.1 (M+H).

Example 19:

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide (18 mg, 6%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (198 mg, 0.513 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (1.03 mL, 3.08 mmol), zinc chloride (70 mg, 0.513 mmol) and 1H-indole-2-carboxylic acid methoxy-methyl-amide (629 mg, 3.08 mmol).

MS ESI : 517.2 (M+H); Structure confirmed by ^{1}H NMR 400 MHz in DMSO.

Example 20:

5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide (9 mg, 3%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (183 mg, 0.476 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (0.95 mL, 2.86 mmol), zinc chloride (65 mg, 0.476 mmol) and 5-chloro-1H-indole-2-carboxylic acid dimethylamide (636 mg, 2.86 mmol).

MS ESI : 535.2 (M+H); Structure confirmed by ^{1}H NMR 400 MHz in DMSO.

Example 21:

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid dimethylamide (22 mg, 25%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (190 mg, 0.494 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (0.98 mL, 2.96 mmol), zinc chloride (67 mg, 0.494 mmol) and 5-fluoro-1H-indole-2-carboxylic acid dimethylamide (613 mg, 2.96 mmol).

MS ESI : 519.3 (M+H); Structure confirmed by ^{1}H NMR 400 MHz in DMSO.

Example 22:

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid N,N'-dimethyl-hydrazide (13mg, 6%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (160 mg, 0.416 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (0.83 mL, 2.49 mmol), zinc chloride (57 mg, 0.416 mmol) and 1H-indole-2-carboxylic acid N,N'-dimethyl-hydrazide (507 mg, 2.49 mmol).

MS ESI : 516.2 (M+H).

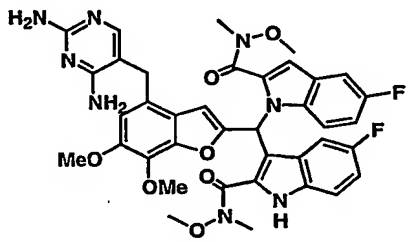
Example 23:

5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide (8 mg, 2.5%) was obtained by reacting 5-(2-chloromethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine (216 mg, 0.560 mmol) with a 3M-solution of ethyl magnesium bromide in diethyl ether (1.08 mL, 3.24 mmol), zinc chloride (76 mg, 0.560 mmol) and 5-chloro-1H-indole-2-carboxylic acid methoxy-methyl-amide (771 mg, 3.24 mmol).
MS ESI : 552.1 (M+H).

Example 24: See **Scheme 3**

To a solution of [4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-yl]-methanol (1 eq, 2.74 g, 8.3 mmol) in chloroform, Manganese oxide (10 eq, 7.22 g, 83 mmol) was added at room temperature under Argon. The reaction mixture was heated at 45°C. After completion of the reaction, the hot mixture is filtered through 7 filter papers. The Manganese oxide residue is washed with hot acetonitrile.
The filtrate is evaporated to give 4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-carbaldehyde as a yellow solid (1.63 g, 60%).

To a suspension of 4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-carbaldehyde (1 eq, 190 mg, 0.58 mmol) and 5-fluoro-1H-indole-2-carboxylic acid methoxy-methyl-amide (2 eq, 886 mg, 1.74 mmol) in Acetic acid (C=0.20 M), a 30% solution of HBr in acetic acid (10 eq, 1.2 mL) was added slowly at 5 °C under Argon. The purple mixture was stirred 20 minutes under Argon until completion.
The resulting mixture was poured onto ice water, basified until pH 8 by adding a solution saturated of $NaHCO_3$. After centrifugation of the resulting suspension was filtered and the resulting precipitate was lyophilized overnight. The residue was then digested in methanol to precipitate the amide in excess (this operation is done three times). After filtration, the filtrate was evaporated to give the compound of formula **XIV**. This compound was used for the next step without further purification.



XIV

To a solution of the dimere adduct **XIV** (1 eq) in trifluoroacetic acid, boron trifluoride-ethyletherate (3 eq) and triethylsilane (3 eq) were added at 0°C under Argon. The reaction mixture was then heated at 30°C until completion. The resulting mixture was poured onto ice, potassium carbonate was added until pH 8. Sodium acetate was added to saturate the medium and the product was extracted with acetonitrile. The organic layer was evaporated and the residue lyophilized overnight. The precipitate obtained was digested in methanol and the resulting filtrate was evaporated. 3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid methoxy-methyl-amide (8.6 mg, 2.7% over the two steps) was obtained after purification by FC, gradient from CH_2Cl_2 to CH_2Cl_2/methanol (93/7).
MS ESI : 535.5 (M+H)

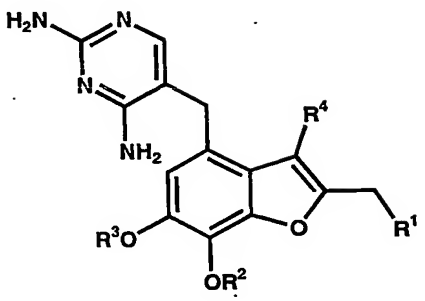
General Procedure E: Measurement of antimicrobial activity

Antimicrobial susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) procedure [M7-A5, 2001].
M7-A5 (2001) : Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard —Fifth Edition American National Standard

General Procedure F: Purified Enzymes and DHFR Enzyme Assay:
Bacterial and human dihydrofolate reductases were purified, shown to be functional and used in DHFR assays as described by Baccanari & Joyner (Baccanari, D.P. and Joyner, S.S. 1981. Dihdrofolate reductase hysteresis and its effect on inhibitor binding analyses. Biochem. 20, 1710-1716)

Claims

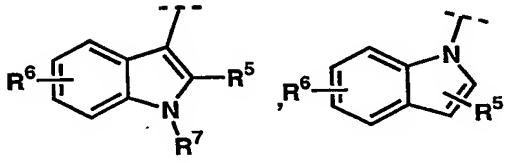
1. Compounds of the general formula I



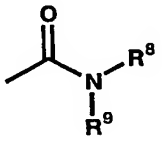
Formula I

wherein

R1 represents the groups



whereby in these groups R^5 is hydrogen, lower alkyl with 1 to 4 carbon atoms, or the group



wherein

R^8 represents hydrogen, lower alkyloxy, lower alkylamino, lower alkyl with 1 to 4 carbon atoms;

R^9 represents hydrogen, lower alkyl with 1 to 4 carbon atoms;

R^8 and R^9 together form a 5- or 6- membered heterocyclic ring containing one to two hetero atoms which can be the same or different and are oxygen or nitrogen.

R^6 represent hydrogen, halogen, nitro, lower alkyloxy, boronic acid;

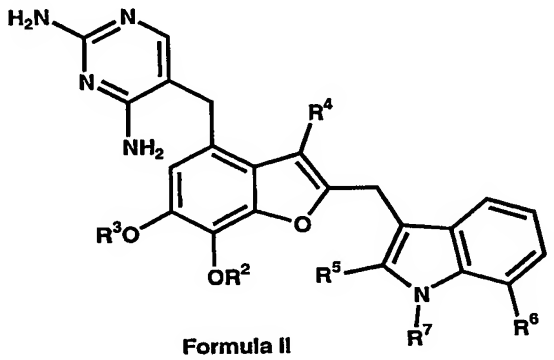
R^7 represents hydrogen;

R^2 and R^3 independently represent hydrogen; lower alkyl with 1 to 3 carbon atoms; or together a lower alkylene group with 1 to 3 carbon atoms bridging the oxygen atoms and forming a five, six or seven membered ring;

R^4 represents hydrogen, lower alkyl with 1 to 4 carbon atoms;

and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula II

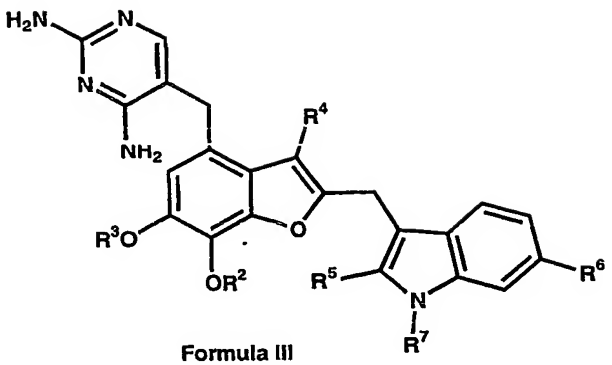


Formula II

wherein
$R^2$and R^3 represent methyl;
R^4 represents hydrogen and
R^5 and R^6 are as defined in formula I;
R^7 represents hydrogen;

and pharmaceutically acceptable salts thereof.

3. Compounds of the general formula III



Formula III

wherein

$R^2$and R^3 represent methyl;

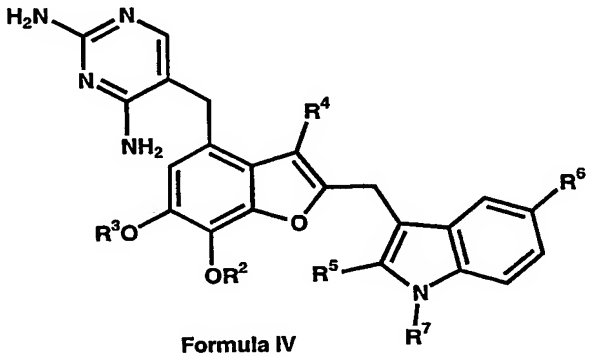
R^4 represents hydrogen and

R^5 and R^6 are as defined in formula I;

R^7 represents hydrogen;

and pharmaceutically acceptable salts thereof.

4. Compounds of the general formula IV



Formula IV

wherein

$R^2$and R^3 represent methyl;

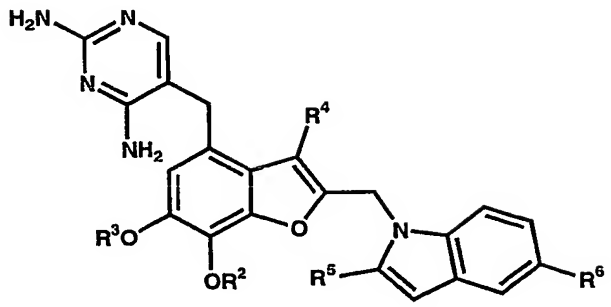
R^4 represents hydrogen and

R^5 and R^6 are as defined in formula I;

R^7 represents hydrogen;

and pharmaceutically acceptable salts thereof.

5. Compounds of the general formula **V**



Formula V

wherein
R^2 and R^3 represent methyl;
R^4 represents hydrogen and
R^5 and R^6 are as defined in formula **I**;

and pharmaceutically acceptable salts thereof.

6. Compounds selected from the group consisting of:

5-(2-Indol(4-boronicacid)-1-ylmethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine;
5-(2-Indol-1-ylmethyl-6,7-dimethoxy-benzofuran-4-ylmethyl)-pyrimidine-2,4-diamine;
5-[6,7-Dimethoxy-2-(7-methoxy-indol-1-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;
5-[6,7-Dimethoxy-2-(5-methoxy-1-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;
5-[2-(1-Indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;
5-[6,7-Dimethoxy-2-(2-methyl-1-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;
5-[2-(5-Bromo-indol-1-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;
5-[2-(6-Fluoro-1-indol-3-ylmethyl)-6,7-dimethoxy-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

{3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl}-morpholin-4-yl-methanone;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-5-boronic acid;

5-[6,7-Dimethoxy-2-(5-nitro-1H-indol-3-ylmethyl)-benzofuran-4-ylmethyl]-pyrimidine-2,4-diamine;

{3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indol-2-yl}-pyrrolidin-1-yl-methanone;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-methoxy-1H-indole-2-carboxylic acid dimethylamide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide;

5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid dimethylamide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid dimethylamide;

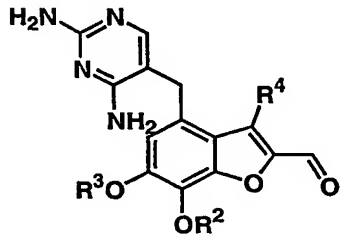
5-Chloro-3-[4-(2,4-diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid methoxy-methyl-amide;

3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-1H-indole-2-carboxylic acid N,N'-dimethyl-hydrazide;

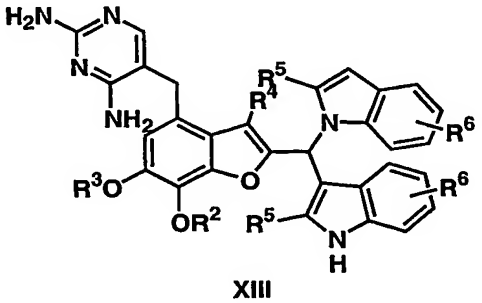
3-[4-(2,4-Diamino-pyrimidin-5-ylmethyl)-6,7-dimethoxy-benzofuran-2-ylmethyl]-5-fluoro-1H-indole-2-carboxylic acid methoxy-methyl-amide;

and pharmaceutically acceptable salts thereof.

7. Intermediates of the general formula **XII** and **XIII**.



XII



XIII

wherein R^2, R^3, R^4, R^5 and R^6 have the meaning given in fomula I in claim 1.

8. Pharmaceutical compositions comprising one or more compounds of any one of claims 1 to 6 and usual inert carrier materials.

9. Pharmaceutical compositions for the treatment of of infections caused by Gram positive or Gram negative pathogens comprising one or more compounds of any one of claims 1 to 6 and usual inert carrier materials.

10. The compounds of any one of claims 1 to 6 for use as medicaments.

11. The compounds of any one of claims 1 to 6 for use as medicaments for the treatment of infection,

12. The compounds of any one of claims 1 to 6 for use as medicaments for the treatment of infection caused by Gram positve or Gram negative pathogens or by a mixture thereof.

13. The use of one or more compounds of any one of claims 1 to 6 as active ingredients for the production of pharmaceutical compositions.

14. The use of one or more compounds of any one of claims 1 to 6 as active ingredients for the production of pharmaceutical compositions for the treatment of infections.

15. The use of one or more compounds of any one of claims 1 to 6 as active ingredients for the production of pharmaceutical compositions for the treatment of infections caused by Gram positive or Gram negative pathogens or by a mixture thereof.

16. A process for the manufacture of pharmaceutical compositions containing one or more compounds as claimed in any one of claims 1 to 6 as active ingredients which process comprises mixing one or more active ingredients with pharmaceutically acceptable inert carrier materials and adjuvants in a manner known per se.

17. A process for the manufacture of pharmaceutical compositions for the treatment of infections caused by Gram positive or Gram negative pathogens or by a mixture

thereof containing one or more compounds as claimed in any one of claims 1 to 6 as active ingredients which process comprises mixing one or more active ingredients with pharmaceutically acceptable inert carrier materials and adjuvants in a manner known per se.

Abstract

The invention relates to new benzofuran derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as anti-infectives.